ASEPTIC PROCESSING ANNEX 1 HIGHLY POTENT BIOPHARMACEUTICALS

ISPE Moscow Conference
16th and 17th of October 2017

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Agenda

1	Updates on Annex 1
2	Highly Potent Aseptic Containment Requirements
3	ADC Processing. Technical Solutions for operator and product protection
4	Occupational Hygienic Validation/ Cleaning Validation
5	Question and Answer

New Annex 1

- Not yet released
- Industry is waiting for the draft to provide comments
- Latest Information from the PDA Workshop in Washington DC on the 2nd and 3rd October.
- Reasons for the update. Quality Risk Management, New Technologies like Single Used Closed Systems, Disposables, Robotics……
- Operators should not have access to Grade A as they are the highest risk of Contamination

GMP Requirements

- No humans close to grade A (ISO 5) Area

Facilities

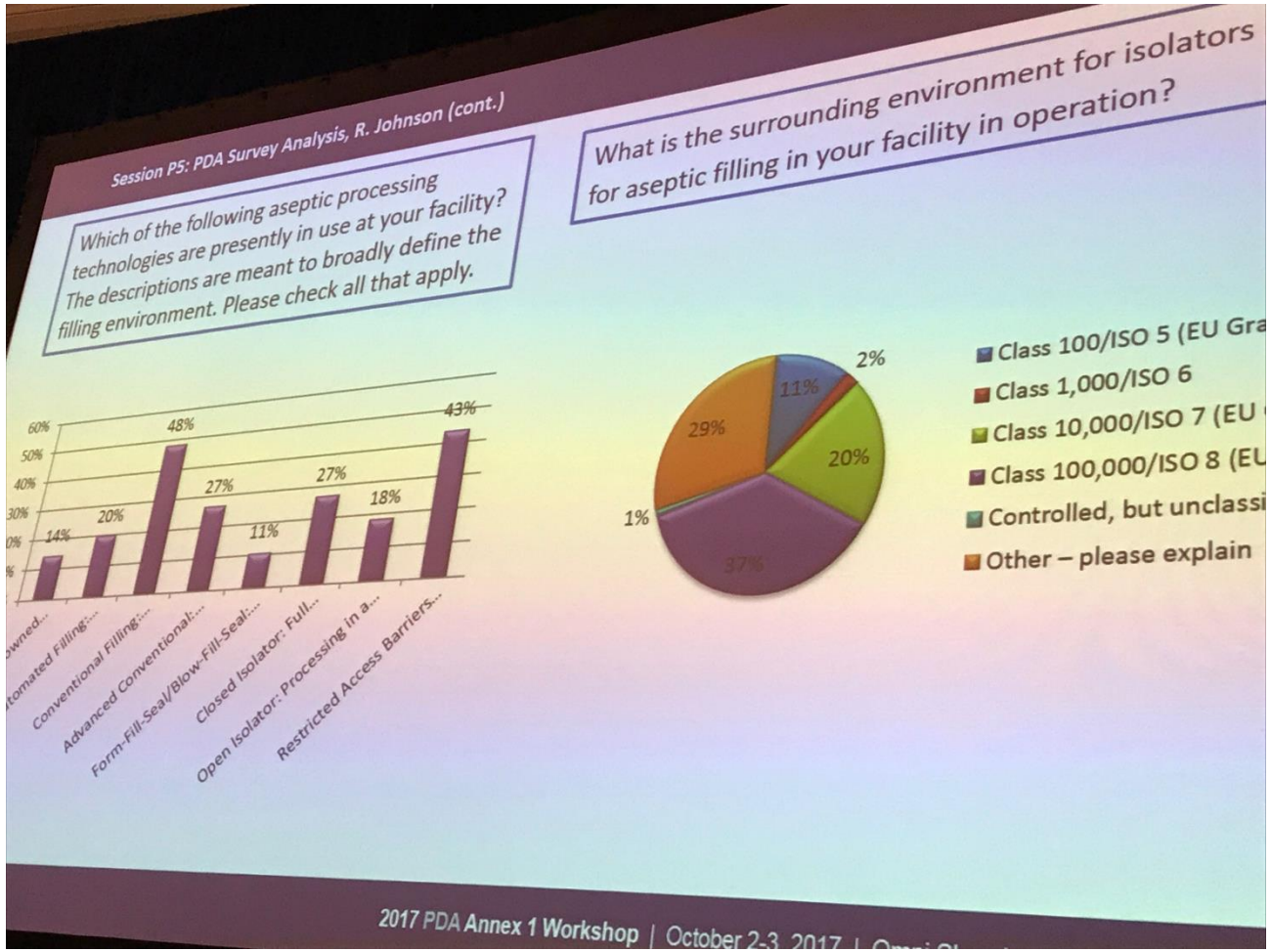
Conventional Aseptic Processing
Highest risk of human intervention

RABS «Restricted Access Barrier System»
Reduced risk of human intervention

Isolators
Lowest risk of human intervention

New Annex 1

- No humans close to grade A (ISO 5) Area



PDA Survey
Introduced during the Annex 1 Workshop in Washington DC on the 2nd and 3rd of October

GMP Requirements

- No humans close to grade A (ISO 5) Area

Facilities

Conventional Aseptic Processing
Highest risk of human intervention

Conventional Solution

- Operator have access to critical areas
- No Barrier
- Contamination Risk on the Curtain.
- Intensive Training and Monitoring
- Technology should be replaced to better ones.

GMP Requirements

- No humans close to grade A (ISO 5) Area

RABS " Restricted Access Barrier System"

- Operator have access to critical areas
- Barrier but doors can be opened
- Decontamination inside of the door before closing.
- Intensive Training and Monitoring
- More and more poor designed RABS on the market.

RABS «Restricted Access Barrier System»
Reduced risk of human intervention

GMP Requirements

- No humans close to grade A (ISO 5) Area

Serious FDA Warning Letter issued to European Manufacturer of sterile Drugs, Part 2

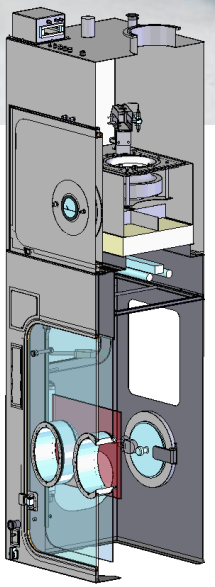
In case of serious violations of GMP requirements, the American FDA issues a Warning Letter to the company in question. The company must react to this within 15 working days and submit a corrective action plan to the FDA.

Two aspects were criticized with regard to 21 CFR 211.113: "inadequate aseptic techniques" and "mechanical faults during media fill". The inspector supported the "inadequate aseptic techniques" with a video recording of a line set-up followed by the filling. It showed the following incorrect behaviour:

- an employee handed a pen to another employee directly above the stopper bowl
- an employee was sitting on the floor during line set-up and did not change his gown afterwards
- an employee was leaning against the cleanroom wall
- an employee left the door of an RABS open for a considerable time during the filling without working in the immediate area

GMP Requirements

- No humans close to grade A (ISO 5) Area



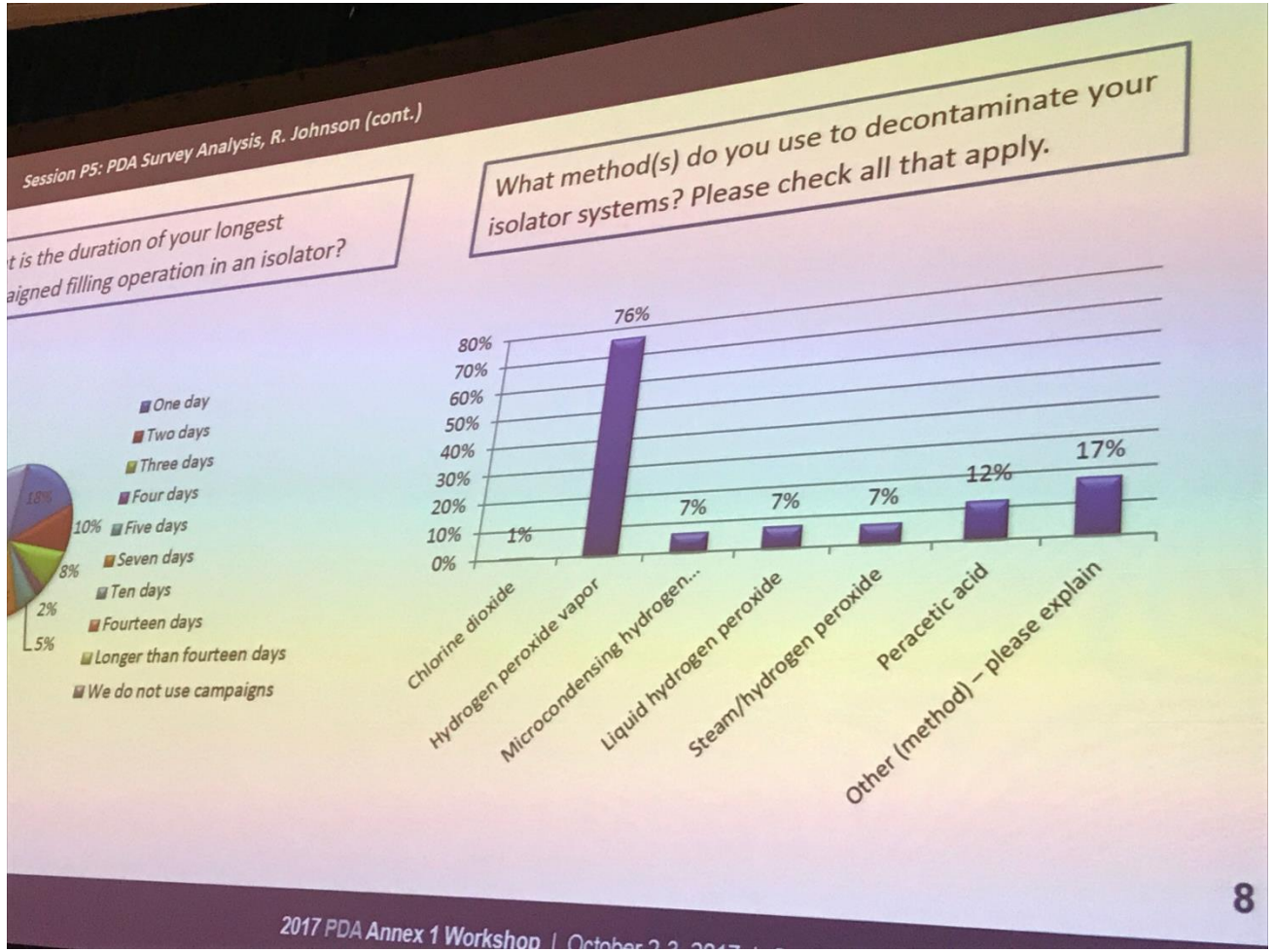
Isolators

- Operator have no direct access to critical areas
- Validated and accepted decontamination system with H_2O_2
- Reduced Clean Room requirements outside of the Isolator (ISO 7/8 Class C/D)
- Less Gowning of the Operator
- More and more poor designed Isolators on the market. High risk to the product

Isolators
Lowest risk of human intervention

GMP Requirements

- No humans close to grade A (ISO 5) Area



PDA Survey
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Key Reason for Update

Annex 1 update

Key reasons for update

- Contamination control strategy
  - Linked to 3.6, 5.20, 5.21
  - Understand facility
  - Understand Equipment
  - Understand process
  - Update based on feedback

Andrew Hopkins
Introduced during the Annex 1 Workshop in Washington DC on the 2nd and 3rd of October

MHRA
Regulating Medicines and Medical Devices

Chapter 5.20: New Requirements Based on the EMA Guideline on Setting Health-Based Exposure Limits in shared facilities based on the PDE „Permitted Daily Exposure“

Chapter 5.21: “Depending on the contamination risk, verification of cleaning of non- product contact surfaces and monitoring of air within the manufacturing area [...] in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer.”

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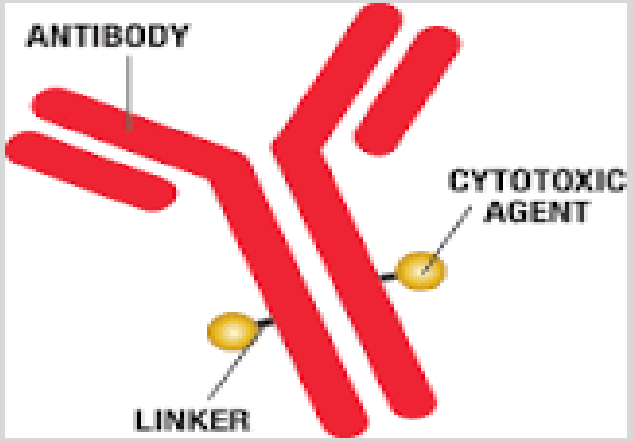
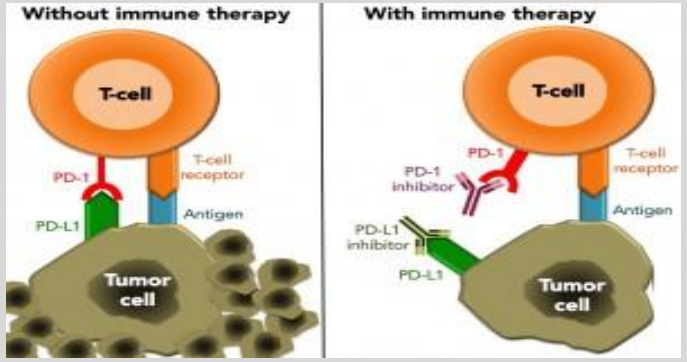
Highly Potent Biological Anti Cancer Treatments

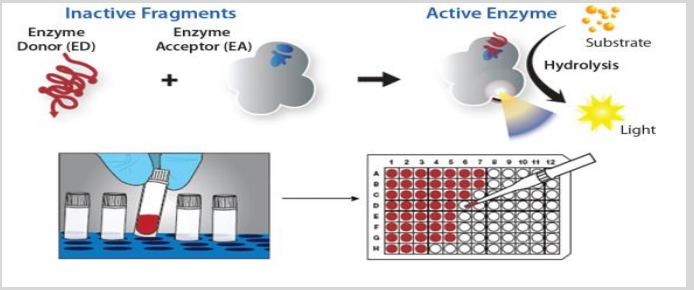
ADCs (Antibody Drug Conj.)

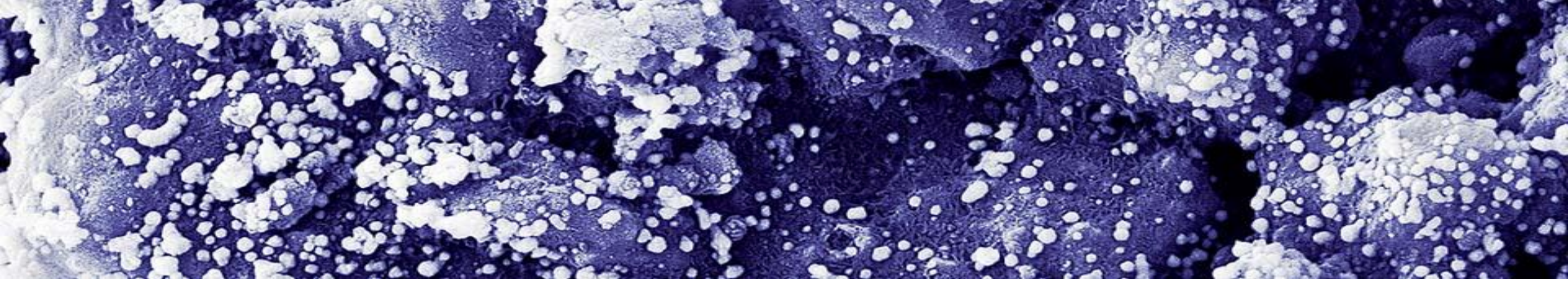


Regenerative Medicine Immune-Gene-Cell Therapy



HPBs (Highly Potent Bios)

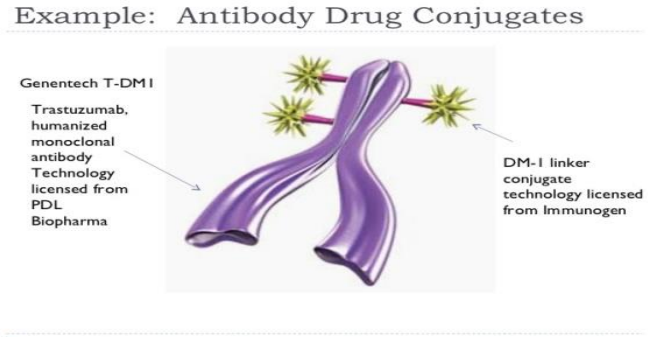


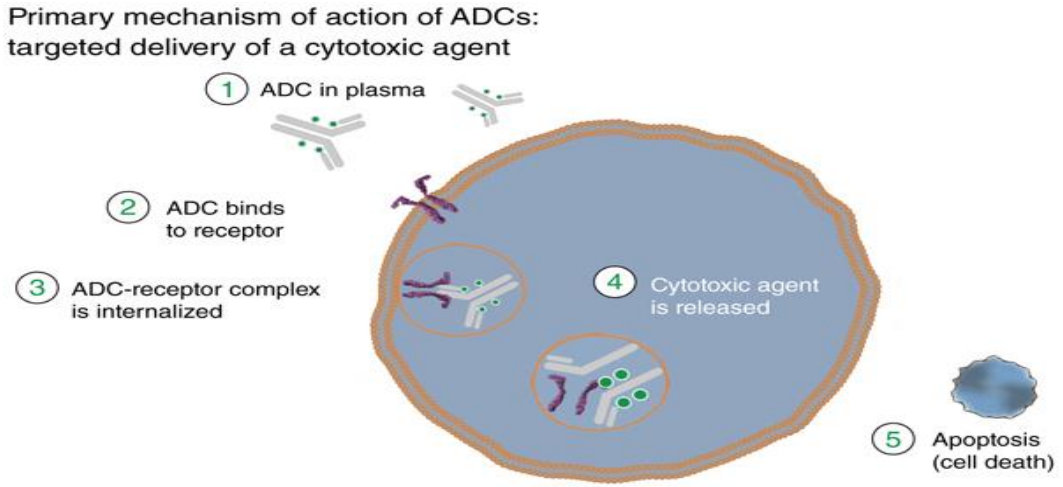


What is an Antibody Drug Conjugates ADCs and why is it so high potent ?

Warhead *Often a highly hazardous substance

Payload = Warhead + Linker





Highly Potent Biological Anti Cancer Treatments

Protect the Patient & Protect the Operator

The overall driver for equipment & facility is the level of potency of the API payload and the level of potency of the combined product.

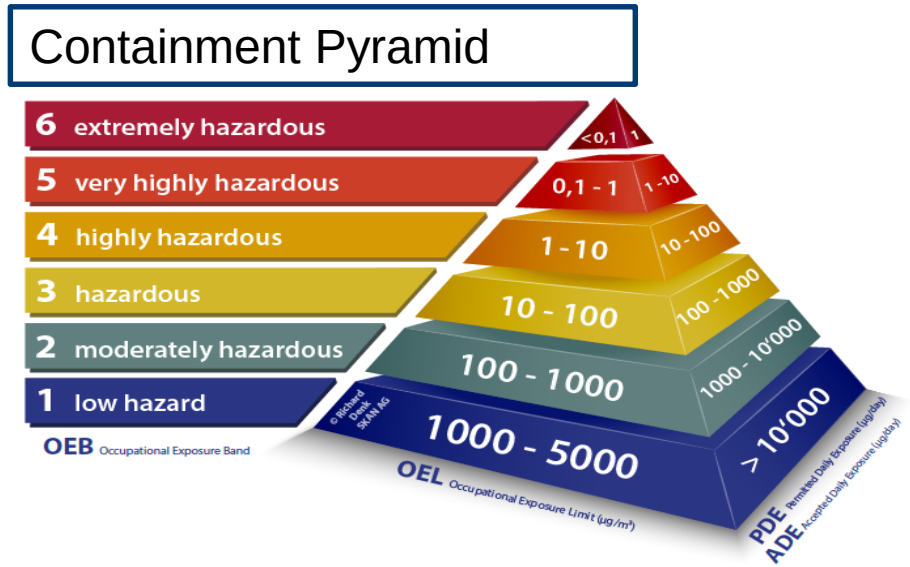
Operator & patient exposure needs to be understood and controlled appropriately.

Highly Potent Aseptic Products Containment Requirements

Highly Potent Aseptic Containment Requirements

The requirements placed on closed systems / containment are increasing.

Systems must be classified by means of approved limit values.



ADCs Containment Requirements

What does OEL/OEB mean?

»OEL (Occupational Exposure Limit)

Defines an average concentration load of a drug or API measured over a particular time.

The measurement is carried out in the employee´s breathing area over a period of eight hours (40 hour week). The term OEL comes from the pharmaceutical industry, where internal occupational exposure limits have been calculated for a long time without being regulated by the authorities.

»OEB (Occupational Exposure Band)

It considers the toxicology of the pure substance. The aim is to provide a system categorisation that can be used to select a suitable production facility and working procedure for a product.

Containment: New Requirements Based on the EMA Guideline on Setting Health-Based Exposure Limits

New EMA Requirements

Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

- Why new Requirements like the PDE (Permitted Daily Exposure) needed?
- No clear definition on which products can be manufactured in shared facilities
- Parameters like the 10ppm or 1/1000 therapeutic dose were not sufficient anymore.

New EMA Requirements

Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

- The risk cannot be adequately controlled by operational and/or technical measures,
- Scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising material such as beta lactams)
- Relevant residue limits, derived from the toxicologic evaluation, cannot be satisfactorily determined by a validated analytical method

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ADC Process: Dispensing, Conjugation and Purification

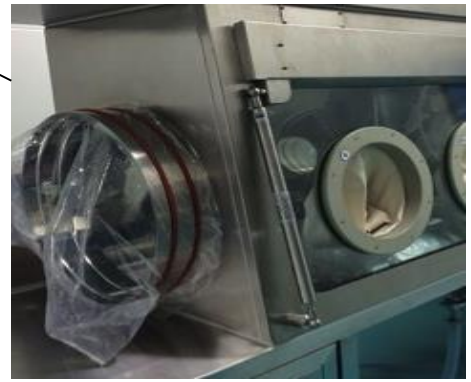
Non Aseptic and Toxic Bulk

Scaling and dispensing

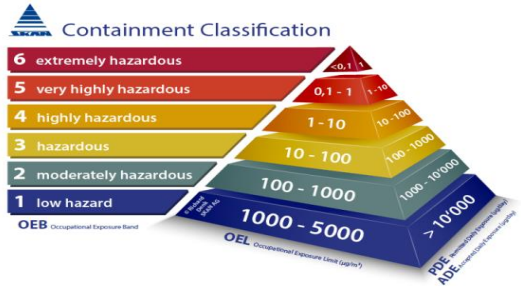
Conjugation

Purification

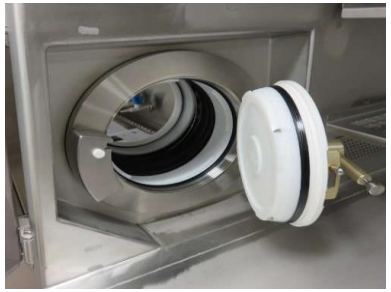
Freezing



Isolator for Purification.



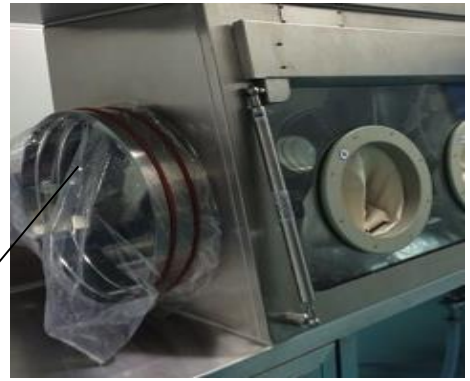
Filter (Containment)
FiPa



RTP
Material in/out etc.

ADC Process: Sterile Filtration and Fill & Finish

- Aseptic ADC
- Thawing
- Sterile Filtration
- Fill & Finish
- Sterility test



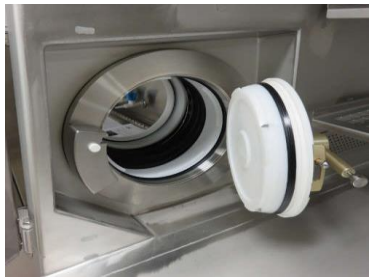
Isolator for sterile filtration

SART connector

ADC Process: Sterility Test

- Aseptic ADC
- Thawing
- Sterile Filtration
- Fill & Finish
- Sterility test

SARA
Tools/Waste etc.



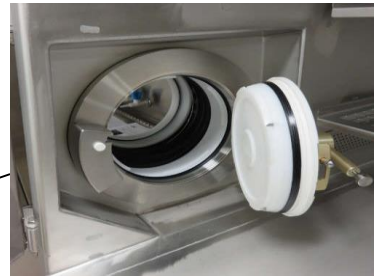
ADC Process: Storage, Inspection and Packaging

Aseptic ADC

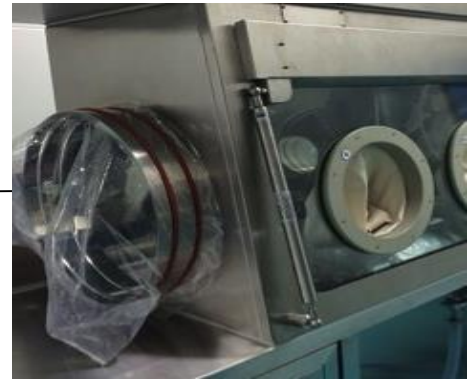
Storage final Product

Inspection

Packaging



Storage Transfer



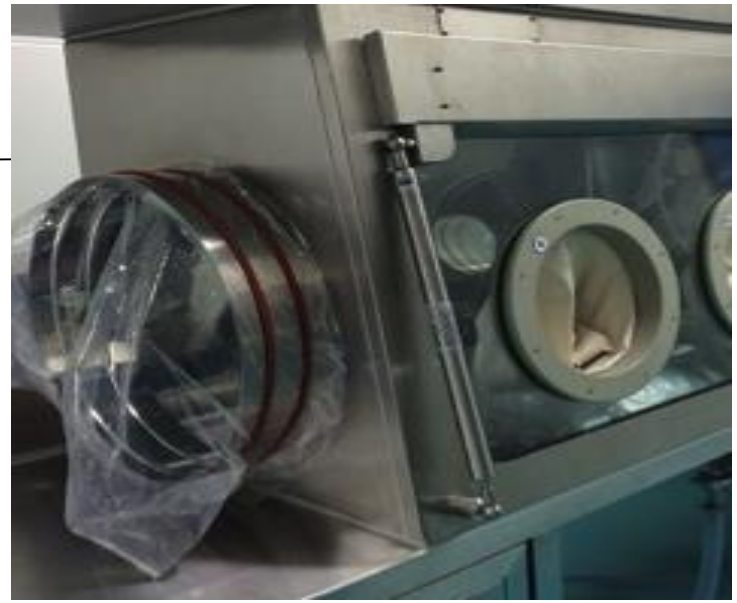
Isolator for Inspection

Isolator for Packaging

ADC Process: Cleaning of Process Parts

Aseptic ADC

Off Line Cleaning



Isolator for Cleaning

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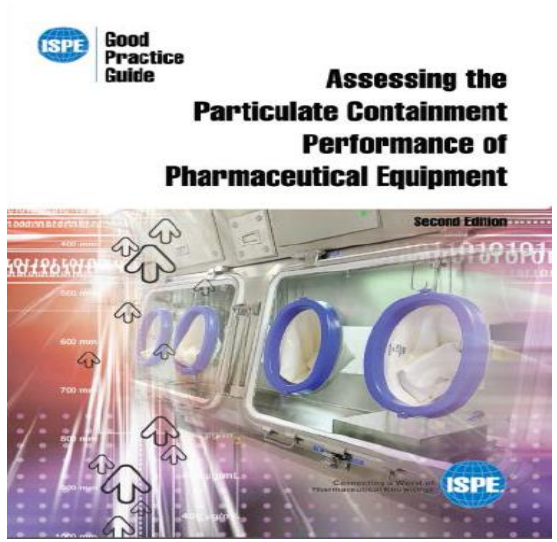
Occupational Hygienic Validation/ Cleaning Validation

How to measure Containment ?

SMEPAC Good Practise Guide

SMEPAC (Standardized Measurement of Equipment Particulate Containment)



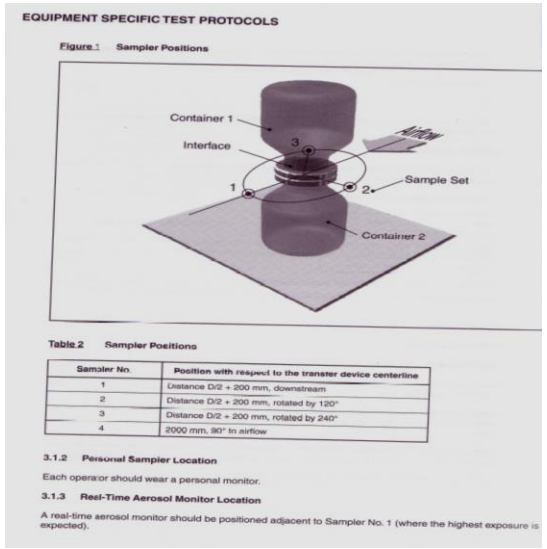

EQUIPMENT SPECIFIC TEST PROTOCOLS

Figure 1 Sampler Positions

Table 2 Sampler Positions

Sampler No.	Position with respect to the transfer device centerline
1	Distance D/2 + 200 mm, downstream
2	Distance D/2 + 200 mm, rotated by 120°
3	Distance D/2 + 200 mm, rotated by 240°
4	2000 mm, 90° to airflow

3.1.2 Personal Sampler Location

Each operator should wear a personal monitor.

3.1.3 Real-Time Aerosol Monitor Location

A real-time aerosol monitor should be positioned adjacent to Sampler No. 1 (where the highest exposure is expected).

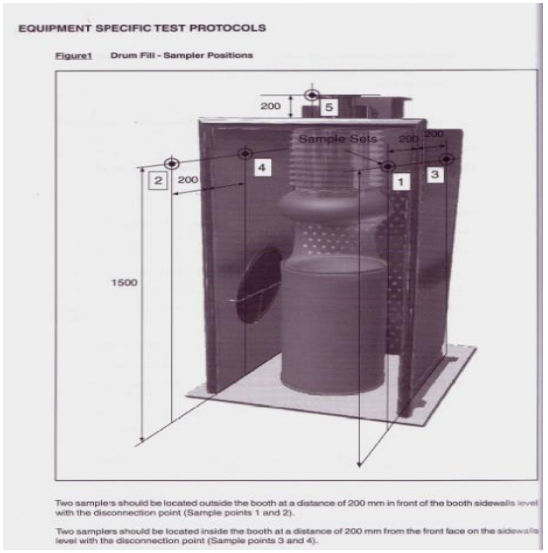

EQUIPMENT SPECIFIC TEST PROTOCOLS

Figure 1 Drum Fill - Sampler Positions

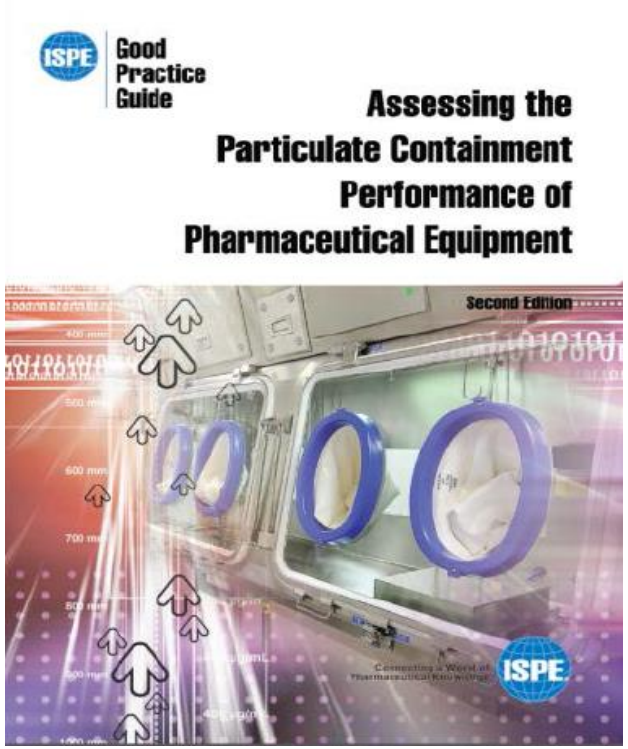
Two samplers should be located outside the booth at a distance of 200 mm in front of the booth sidewalls level with the disconnection point (Sample points 1 and 2).

Two samplers should be located inside the booth at a distance of 200 mm from the front face on the sidewalls level with the disconnection point (Sample points 3 and 4).

How to measure Containment ?

Challenge: SMEPAC does not cover Aseptic Manufacturing

Aseptic Manufacturing is the Champions League on Containment.



New Method “Occupational Hygiene Validation”

1	**Occupational Hygiene Validation on Fill & Finish Lines**	
	1.1	Explanation of the filling line
	1.2	PDE/OEL Requirements
	1.3	Method of the Containment Performance
	1.4	Surrogate Test Product
	1.5	Risk Assessment
	1.6	Used Containment Barrier
	1.7	Location of the Air Samplers and Wipe Positions
	1.8	Training and Good Housekeeping
	1.9	Execution of the Occupational Hygiene Validation
	1.10	Results / Deviation

Cleaning Method

GMP product and operator protection and cleaning requirements of non-product-contact surfaces in aseptic Isolators.

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Dr. Andreas Flückiger, F. Hoffmann-La Roche Ltd, (CH)
Hirokazu Kisaka, Takeda (JP)
Dr. Reinhold Maeck, Boehringer Ingelheim GmbH, (D)
Dr. Lars Restetzki, F. Hoffmann-La Roche Ltd, (CH)
Dr. Andreas Schreiner, Novartis, (CH)
Rico Schulze, GMP Inspectorate at Landesdirektion Sachsen, (D)

Validation of the cleanliness of non-product-contact surfaces has increased in popularity since the EMA proposed the following measures in order to demonstrate effective management of the cross-contamination risk (in Chapter 5.21 of Part 1 of its GMP guidelines): **“Depending on the contamination risk,** verification of cleaning of non- product contact surfaces and monitoring of air within the manufacturing area [...] in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer.”

Cleaning Method

Steps of the Cleaning Method of non- product contact surfaces within aseptic Isolators:

- Risk identification based on the layout, Air Flow Simulation, routine operations within the isolator with gloves, Riboflavin Study.
- Cleaning requirements based on the ADE/PDE
  - Manual Cleaning
  - Semi automated cleaning
  - Fully automated cleaning
- Cleaning Method to demonstrate the effectiveness of the cleaning.
- Cleaning from less critical areas towards critical areas.
- Route of waste material

ISPE. | Germany | Austria | Switzerland Affiliate

ISPE D/A/CH Affiliate: Containment Manual

(English Translation)

https://www.ispe.org/publications/guidance-documents/topic

Thank you!

Questions?